

WO9933794A1: .ohgr.-CYCLOALKYL-PROSTAGLANDIN E2 DERIVATIVES

[View Images \(108 pages\)](#) | [View Cart](#)

Premium Data ¹: [PDF \(~10300 KB\)](#) | [TIFF \(~8100 KB\)](#) | [Fax](#) | [More choices...](#)

Inventor(s): TANI, Kousuke , Ono Pharmaceutical Co., Ltd., Minase Research Institute, 1-1, Sakurai 3-chome, Shimamoto, Japan
OHUCHIDA, Shuichi , Ono Pharmaceutical Co., Ltd., Minase Research Institute, 1-1, Sakurai 3-chome, Shimamoto, Japan

Applicant(s): ONO PHARMACEUTICAL CO., LTD., 1-5, Doshomachi 2-chome, Chuo-ku, Osaka-shi, Osaka541-8526, Japan

Issued/Filed Dates: July 8, 1999 / Dec. 24, 1998

Application Number: WO1998JP0005863

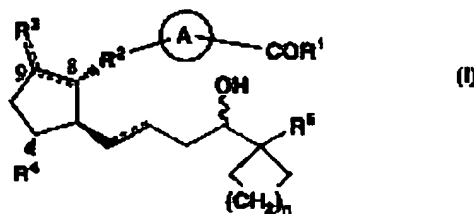
IPC Class: C07C 405/00;

Designated JP, KR, US, **European patent:** AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, **Countries:** LU, MC, NL, PT, SE

Abstract: .ohgr.-Cycloalkyl-prostaglandin E2 derivatives of formula (I) (wherein all symbols are as defined in the description); and non-toxic salts thereof, prodrugs thereof and cyclodextrin clathrates thereof. Compounds of formula (I) strongly bind on the EP2 subtype receptor. Therefore, they are useful for prevention and/or treatment of immunological diseases (autoimmune diseases, organ transplantation, etc.), asthma, abnormal bone formation, neuronal cell death, liver damage, abortion, premature birth or retina neuropathy of glaucoma, etc.

[\[Show "fr" Abstract\]](#)

**Representative
Image:**



Attorney, Agent, or Firm: OHIE, Kuniyisa;
Foreign References: none

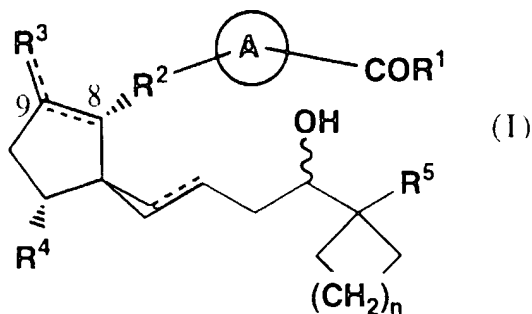
(No patents reference this one)

DB7



CLAIMS

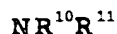
1. An ω -cycloalkyl-prostaglandin E₂ derivative of formula (I)



5

[wherein A is benzene, thiophene or furan ring;
R¹ is hydroxy, C1-6 alkoxy or a group of formula

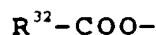
10



(wherein R¹⁰ and R¹¹ are each independently, hydrogen atom or C1-4 alkyl));

R² is C1-4 alkylene, C2-4 alkenylene, -S-C1-4 alkylene, -S-C2-4 alkenylene or C1-4 alkylene-S-;

15 R³ is oxo, methylene, halogen atom or a group of formula



(wherein R³² is C1-4 alkyl, C1-4 alkoxy, phenyl, phenyl-C1-4 alkyl, R³²-OOC-C1-4 alkyl or R³²-OOC-C2-4 alkenyl (wherein R³² is hydrogen
20 atom or C1-4 alkyl));

R⁴ is hydrogen atom, hydroxy or C1-4 alkoxy;

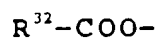
R⁵ is C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, or C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted by 1-3 substituents selected from (1)-(5) below:

- 25 (1) halogen atom,
(2) C1-4 alkoxy,
(3) C3-7 cycloalkyl,

- (4) phenyl or
(5) phenyl substituted by 1-3 substituents selected from halogen atom, C1-4 alkyl, C1-4 alkoxy, nitro or trifluoromethyl);
n is 0-4;

5

- is single bond or double bond,
with the proviso that when the C8-9 position is double bond, R³
is a group of



(wherein R³² is as defined above) and R³ is C1-6 alkoxy]
or a non-toxic salt thereof or a cyclodextrin clathrate thereof.

- 15 2. A compound according to claim 1, wherein A is a benzene ring.

3. A compound according to claim 1 or claim 2, wherein R¹ is C1-4 alkylene or C2-4 alkenylene.

20

4. A compound according to claim 1 or claim 2, wherein R² is -S-C1-4 alkylene, -S-C2-4 alkenylene.

5. A compound according to claim 1 or claim 2, wherein R³ is
25 C1-4 alkylene-S-.

6. A compound according to claim 3, which is

- (1) (11 α , 13E)-9-Oxo-11,16-dihydroxy-17,17-propano-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13-enoic acid,
30 (2) (11 α , 13E)-9-Oxo-11,16-dihydroxy-17,17-propano-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13,19-dienoic acid,
(3) (11 α , 13E)-9-Oxo-11,16-dihydroxy-17,17-propano-19,20-methano-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13-enoic acid,



- (4) (11 α , 13E)-9-Oxo-11,16-dihydroxy-17,17-propano-19-methyl-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13-enoic acid,
(5) (11 α , 13E)-9-Oxo-11,16-dihydroxy-17,17-propano-1,6-(p-phenylene)-2,3,4,5,20-pentananorprost-13-enoic acid,
5 (6) (9 β , 11 α , 13E)-9-Chloro-11,16-dihydroxy-17,17-propano-19,20-methano-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13-enoic acid,
(7) (9 β , 11 α , 13E)-9-Chloro-11,16-dihydroxy-17,17-propano-19-methyl-1,6-(p-phenylene)-2,3,4,5-tetranorprost-
10 13-enoic acid,
(8) (9 β , 11 α , 13E)-9-Chloro-11,16-dihydroxy-17,17-propano-1,6-(p-phenylene)-2,3,4,5,20-pentananorprost-13-enoic acid or
(9) (9 β , 11 α , 13E)-9-Chloro-11,16-dihydroxy-17,17-propano-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13,19-
15 dienoic acid or a methyl ester thereof.

7. A compound according to claim 4, which is

- (1) (11 α , 8Z, 13E)-9-Acetyloxy-11,16-dihydroxy-17,17-propano-7-thia-1,6-(p-phenylene)-2,3,4,5,20-pentananorprost-
20 8,13-dienoic acid methyl ester,
(2) (11 α , 8Z, 13E)-9-Acetyloxy-11,16-dihydroxy-17,17-propano-7-thia-1,6-(p-phenylene)-2,3,4,5-tetranorprost-8,13-dienoic acid methyl ester,
25 (3) (11 α , 8Z, 13E)-9-Acetyloxy-11,16-dihydroxy-17,17-propano-7-thia-1,6-(p-phenylene)-2,3,4,5-tetranorprost-8,13,19-trienoic acid methyl ester,
(4) (11 α , 8Z, 13E)-9-Acetyloxy-11,16-dihydroxy-19-methyl-17,17-propano-7-thia-1,6-(p-phenylene)-2,3,4,5-tetranorprost-8,13-dienoic acid methyl ester or
30 (5) (11 α , 8Z, 13E)-9-Acetyloxy-11,16-dihydroxy-17,17-

propano-19,20-methano-7-thia-1,6-(p-phenylene)-2,3,4,5-tetranorprost-8,13-dienoic acid methyl ester.

8. A compound according to claim 4, which is

- 5 (1) (11 α , 13E)-9-Oxo-11,16-dihydroxy-17,17-propano-7-thia-1,6-(p-phenylene)-2,3,4,5,20-pentanorprost-13-enoic acid,
- (2) (11 α , 13E)-9-Oxo-11,16-dihydroxy-17,17-propano-7-thia-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13-enoic acid,
- 10 (3) (11 α , 13E)-9-Oxo-11,16-dihydroxy-17,17-propano-7-thia-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13,19-dienoic acid,
- (4) (11 α , 13E)-9-Oxo-11,16-dihydroxy-19-methyl-17,17-propano-7-thia-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13-enoic acid or
- 15 (5) (11 α , 13E)-9-Oxo-11,16-dihydroxy-17,17-propano-19,20-methano-7-thia-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13-enoic acid
- or a methyl ester thereof.

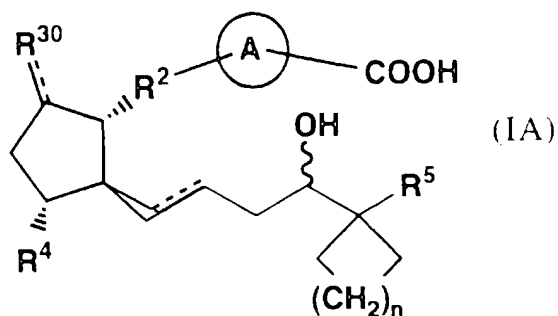
20

9. A compound according to claim 5, which is

- (1) (11 α , 13E)-9-Oxo-11,16-dihydroxy-17,17-propano-6-thia-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13-enoic acid
- or a methyl ester thereof.

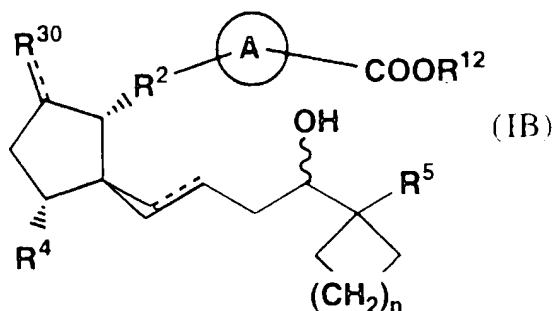
25

10. A process for the preparation of a compound of formula (IA)



(wherein R^1 is oxo, methylene or halogen atom and the other symbols are as defined in claim 1)

characterized by subjecting a compound of formula (IB)



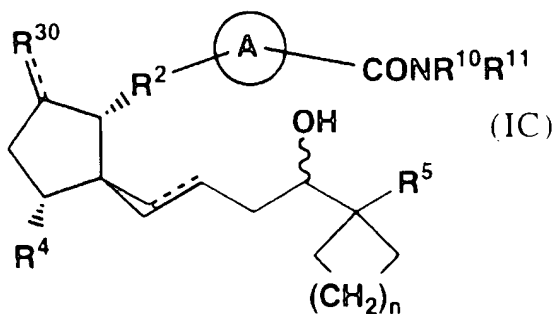
5

(wherein R^1 is C1-6 alkyl and the other symbols are as defined above)

to hydrolysis using an enzyme or hydrolysis under alkaline conditions.

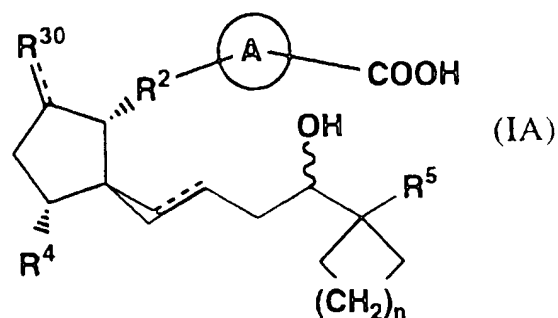
10

11. A process for the preparation of a compound of formula (IC)



15 (wherein R^{30} is as defined in claim 10, and the other symbols are as defined in claim 1)

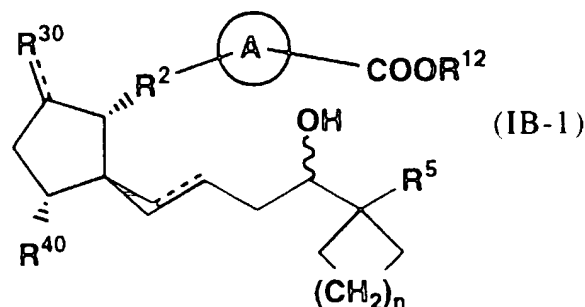
characterized by subjecting to amidation a compound of formula (IA)



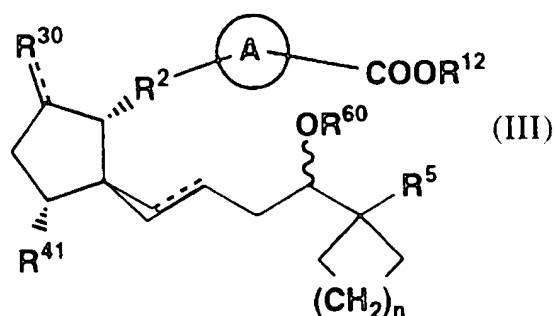
(wherein all symbols are as defined above)
and a compound of formula (II)

5 $HR^{10}R^{11}$ (II)
(wherein all symbols are as defined above).

12. A process for the preparation of a compound of formula
(IB-1)



10 (wherein R^{40} is hydrogen atom or hydroxy, R^{12} and R^{30} are as defined
in claim 10, and the other symbols are as defined in claim 1)
characterized by subjecting to deprotection under acidic
conditions a compound of formula (III)

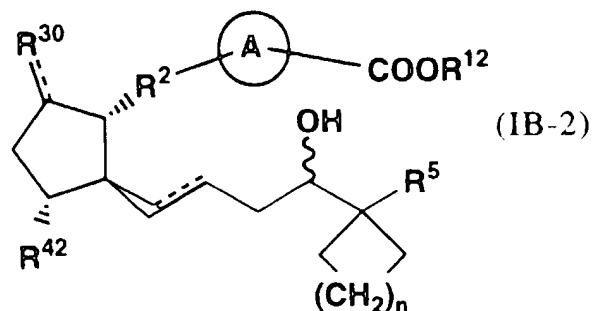


15 (wherein R^{41} is hydrogen atom or hydroxy protected by a group which
may be removable under acidic conditions, R^{60} is a protective group

for hydroxy which may be removable under acidic conditions, and the other symbols are as defined above).

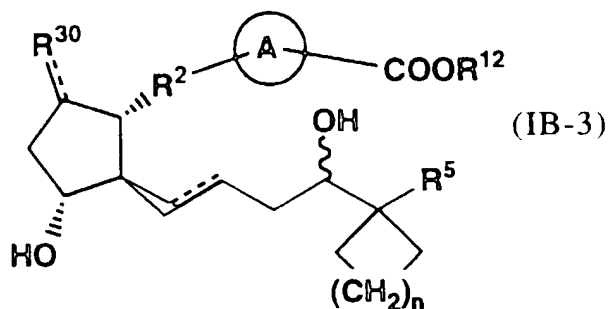
13. A process for the preparation of formula (IB-2)

5



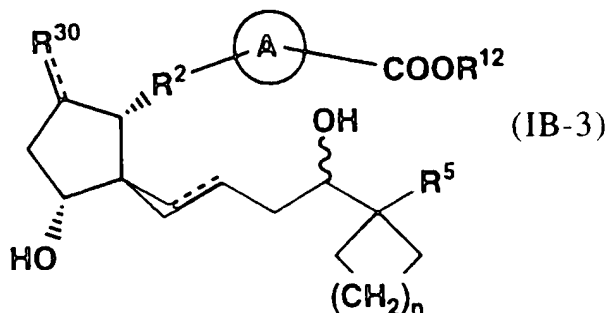
(wherein R^{12} and R^{30} are as defined in claim 10, R^{42} is C1-4 alkoxy, and the other symbols are as defined in claim 1)

10 characterized by subjecting to O-alkylation a compound of formula (IB-3)

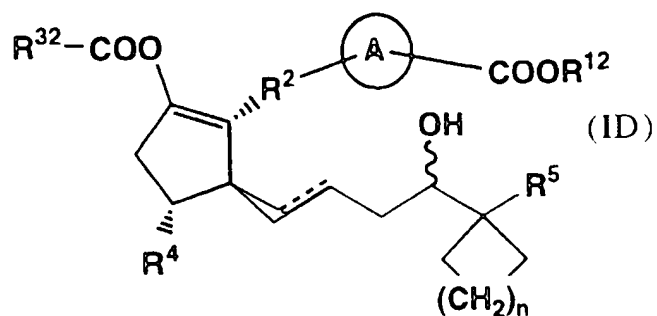


(wherein all symbols are as defined above).

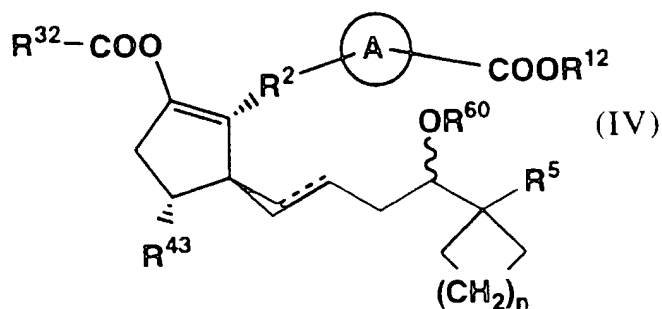
15



14. A process for the preparation of a compound of formula (ID)



- 5 (wherein R^{12} is as defined in claim 10, R^{32} is as defined in claim 1, and the other symbols are as defined in claim 1) characterized by subjecting to deprotection under acidic conditions a compound of formula (IV)



10

(wherein, R^{43} is hydrogen atom, hydroxy protected by a group which may be removable under acidic conditions or C1-4 alkoxy, R^{60} is as defined in claim 12, and the other symbols are as defined above).

INTERNATIONAL SEARCH REPORT

Internat'l Application No

PCT/JP 98/05863

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C405/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 132 738 A (KLUENDER HAROLD C ET AL) 2 January 1979 cited in the application see claims ---	1-14
Y	V. KOZMIK ET AL.: "SYNTZHETIC ANALOGUES OF PROSTAGLANDINS F2ALPHA AND E2" COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS.. vol. 59, 1994, pages 138-148, XP002099715 PRAGUE CS see page 139 -----	1-14

☐ Further documents are listed in the continuation of box C☒ Patent family members are listed in annex.

Special categories of cited documents:

- A: document defining the general state of the art which is not considered to be of particular relevance
- E: earlier document but published on or after the international filing date
- L: document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- O: document referring to an oral disclosure, use, exhibition or other means
- P: document published prior to the international filing date but later than the priority date claimed

- T: later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- X: document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- Y: document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- Z: document member of the same patent family

Date of the actual completion of the international search

14 April 1999

Date of mailing of the international search report

03/05/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk

Authorized officer

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Application No

PCT/JP 98/05863

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4132738 A	02-01-1979	AU 515772 B	30-04-1981
		AU 4449379 A	30-08-1979
		CA 1191132 A	30-07-1985
		DE 2902699 A	30-08-1979
		FR 2430403 A	01-02-1980
		FR 2473509 A	17-07-1981
		GB 2014989 A,B	05-09-1979
		GB 2099814 A,B	15-12-1982
		JP 1194012 C	12-03-1984
		JP 54115351 A	07-09-1979
		JP 58026910 B	06-06-1983
		SE 441673 B	28-10-1985
		SE 7813385 A	24-08-1979
		SE 453990 B	21-03-1988
		SE 8303910 A	08-07-1983
		SE 453830 B	07-03-1988
		SE 8303911 A	08-07-1983
		SE 445109 B	02-06-1986
		SE 8303912 A	08-07-1983
		US 4833157 A	23-05-1989
		US 4331688 A	25-05-1982
		US 4415592 A	15-11-1983
		US 4742080 A	03-05-1988
		US 4275224 A	23-06-1981